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ORIGINAL ARTICLE

Angiographic Severity of the Nonculprit Lesion and the Efficacy of Fractional Flow Reserve–Guided Complete Revascularization in Patients With AMI: FRAME-AMI Substudy

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BACKGROUND: The benefit of fractional flow reserve (FFR)–guided percutaneous coronary intervention (PCI) for noninfarct-related artery (IRA) lesions with angiographically severe stenosis in patients with acute myocardial infarction is unclear.

METHODS: Among 562 patients from the FRAME-AMI trial (Fractional Flow Reserve Versus Angiography-Guided Strategy for Management of Non-Infraction Related Artery Stenosis in Patients With Acute Myocardial Infarction) who were randomly allocated into either FFR-guided or angiography-guided PCI for non-IRA lesions, the current study evaluated the relationship between non-IRA stenosis measured by quantitative coronary angiography (QCA) and the efficacy of FFR-guided PCI. The incidence of the primary end point (death, myocardial infarction, or repeat revascularization) was compared between FFR- and angiography-guided PCI according to non-IRA stenosis severity (QCA stenosis ≥70% or <70%).

RESULTS: A total of 562 patients were assigned to FFR-guided (n=284) versus angiography-guided PCI (n=278). At a median follow-up of 3.5 years, the primary end point occurred in 14 of 181 patients with FFR-guided PCI and 31 of 197 patients with angiography-guided PCI among patients with QCA stenosis ≥70% (8.5% versus 19.2%; hazard ratio, 0.41 [95% CI, 0.22–0.80]; *P*=0.008), while occurred in 4 of 103 patients with FFR-guided PCI and 9 of 81 patients with angiography-guided PCI among those with QCA stenosis <70% (3.9% versus 11.1%; *P*=0.315). There was no significant interaction between treatment strategy and non-IRA stenosis severity (*P* for interaction=0.636). FFR-guided PCI was associated with the reduction of death and myocardial infarction in both patients with QCA stenosis ≥70% (6.7% versus 15.1%; *P*=0.008) and those with QCA stenosis <70% (1.0% versus 9.6%; *P*=0.042) compared with angiography-guided PCI.

CONCLUSIONS: In patients with acute myocardial infarction and multivessel disease, FFR-guided PCI tended to have a lower risk of primary end point than angiography-guided PCI regardless of non-IRA stenosis severity without significant interaction.

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Key Words: coronary angiography ■ drug-eluting stents ■ myocardial infarction ■ percutaneous coronary intervention ■ prognosis

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WHAT IS KNOWN

- Complete revascularization can improve the clinical outcome in patients with acute myocardial infarction and multivessel disease; however, the benefit of fractional flow reserve–guided complete revascularization according to disease severity in these patients is uncertain.

WHAT THE STUDY ADDS

- The current study shows that patients treated with fractional flow reserve–guided complete revascularization showed a lower incidence of death, myocardial infarction, or repeat revascularization than those treated with angiography-guided complete revascularization regardless of noninfarct-related artery stenosis severity without significant interaction.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
FFR	fractional flow reserve
HR	hazard ratio
IRA	infarct-related artery
MI	myocardial infarction
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography

A significant proportion among the patients with acute myocardial infarction (AMI) has multivessel disease, with stenoses in coronary arteries other than the infarct-related artery (IRA), leading to increased mortality rates.[1] Studies have shown that complete revascularization, involving both the IRA and non-IRA, can reduce mortality and recurrent myocardial infarction (MI) rates in these patients.[2,3]

An appropriate evaluation of non-IRA and determining whether to perform percutaneous coronary intervention (PCI), therefore, is crucial to minimize stent implantation and reduce medical costs for patients with AMI and multivessel disease. The current guidelines recommend fractional flow reserve (FFR) measurement when there is no evidence of lesion-specific myocardial ischemia,[4] yet, the data regarding the usefulness of FFR-guided PCI on non-IRA in patients with AMI are limited. Recently, FRAME-AMI trial (Fractional Flow Reserve Versus Angiography-Guided Strategy for Management of Non-Infraction Related Artery Stenosis in Patients With Acute Myocardial Infarction) demonstrated that FFR-guided PCI could reduce the risk of major cardiovascular events in patients with AMI and multivessel disease, compared with angiography-guided PCI.

However, recent studies that demonstrated the usefulness of PCI on non-IRA compared with IRA-only PCI in ST-segment–elevation myocardial infarction (STEMI) with multivessel disease have used angiographic stenosis of >50% to 70% by visual estimation as the cutoff for PCI.[3,5,6] Additionally, compared with patients with stable angina, patients with AMI have more vulnerable plaque features in the non-IRA[7] and have a higher risk of future cardiovascular events even with negative FFR (>0.80).[8]

Therefore, it is uncertain whether FFR-guided PCI will be useful among patients with AMI and non-IRA with angiographically severe stenosis, which carries a high risk of major adverse cardiovascular events due to a large plaque burden. To address this uncertainty, we compared angiography-guided PCI to FFR-guided PCI in patients with AMI and multivessel disease according to nonculprit lesion stenosis measured by quantitative coronary angiography (QCA).

METHODS

The data that support the findings of this study are available from the executive committee upon reasonable request.

Study Design

FRAMI-AMI is a randomized, open-label, multicenter trial conducted from 14 sites located in Korea involving patients with AMI and multivessel coronary artery disease. The patients with STEMI or non–ST-segment–elevation MI aged 19 years and above who successfully underwent primary or immediate PCI, as well as have at least 1 non-IRA lesion with diameter stenosis >50% by the visual estimation at major epicardial coronary artery or major side branch with a vessel diameter of ≥2.0 mm were enrolled. Exclusion criteria are the following: (1) single-vessel disease, (2) flow-limiting stenosis with TIMI flow grade ≤2 in the non-IRA, (3) target lesion located in the left main coronary artery, (4) cardiogenic shock, and (5) chronic total occlusion in non-IRA. Eligible patients were randomly assigned to receive FFR-guided PCI or angiography-guided PCI in a 1:1 ratio. The detailed study design and inclusion-exclusion criteria have been previously published.[9] The study protocol was approved by the institutional review board at each participating site, and all study subjects were provided with written informed consent form before randomization.

Angiographic Analysis

The central angiographic core laboratory at Samsung Medical Center in Seoul, Korea, received anonymized coronary angiography data, including index PCI for STEMI or non–ST-segment–elevation MI, non-IRA PCI, and unscheduled coronary angiography or PCI after index hospitalization. Patients with QCA ≥70% in 1 lesion or more of non-IRA were grouped into QCA ≥70%. QCA was not performed during index PCI for IRA of AMI or angiography/FFR-guided PCI of non-IRA and did not influence the decision to perform PCI or FFR. QCA was measured post procedure, collected in the core laboratory, and categorized into subgroups of ≥70% and <70%.

Treatment

In the angiography-guided PCI group, subjects with lesions with >50% diameter stenosis on visual estimation received PCI. In the FFR group, patients with lesions with FFR of ≤0.80 were treated with PCI. The FFR measurement was done using a pressure-sensor guidewire (CertusTM, Abbott Vascular or PrestigeTM, Philips Volcano) in all non-IRA lesions of >50% stenosis on visual estimation. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg per min^{-1}) or intracoronary nicorandil (2 mg).[10] Only lesions with FFR of ≤0.80 were treated with PCI. Both groups were advised to complete revascularization during the index procedure, but operators had the option to do a staged procedure. After revascularization, patients received guideline-directed medical treatment and were recommended dual antiplatelet therapy for at least 12 months.[11] Clinical follow-ups were done on outpatient clinic visits at 1, 6, 12 months, and annually thereafter. Detailed treatment strategies have been previously published.[9]

Outcomes and Definitions

The primary outcome was a composite of risk of death, MI, and repeat revascularization. Secondary outcomes included all-cause death, cardiac death, MI, procedure-related MI, spontaneous MI, revascularization for IRA, and revascularization for non-IRA. Detailed definitions of each clinical event have been previously published.[9]

Statistical Analysis

Analyses were conducted on an intention-to-treat basis, with all patients analyzed according to their assigned treatment group. Continuous variables were compared using Student *t* test or Mann-Whitney *U* test and presented as mean±SD or median (interquartile range). Categorical data were analyzed using the χ^2 test or Fisher exact test and presented as numbers and percentages. The cumulative incidence of clinical events was presented as a Kaplan-Meier estimate and compared using a log-rank test. Multivariable Cox proportional hazard regression models adjusting for confounders associated with the primary outcome were used to compare ischemic events between angiography-guided PCI and FFR-guided PCI, with hazard ratios (HRs) and 95% CIs calculated after stratifying into QCA ≥70% and <70%. The proportional hazards assumption was evaluated with a 2-sided score test of the scaled Schoenfeld residuals over time at the 0.05 level. Event-free survival with incomplete follow-up was counted as censored data for all time-to-event analyses. Absolute risk differences for ischemic events were calculated with Kaplan-Meier estimates and Greenwood standard errors, with interaction *P* values on the absolute scale calculated using Z tests to assess the differences in absolute risk differences between patients with QCA ≥70% and <70%. All probability values were 2 sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using R Statistical Software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

From August 2016 to December 2020, a total of 562 patients with AMI and multivessel disease were enrolled in the study. Among them, 284 were assigned to the

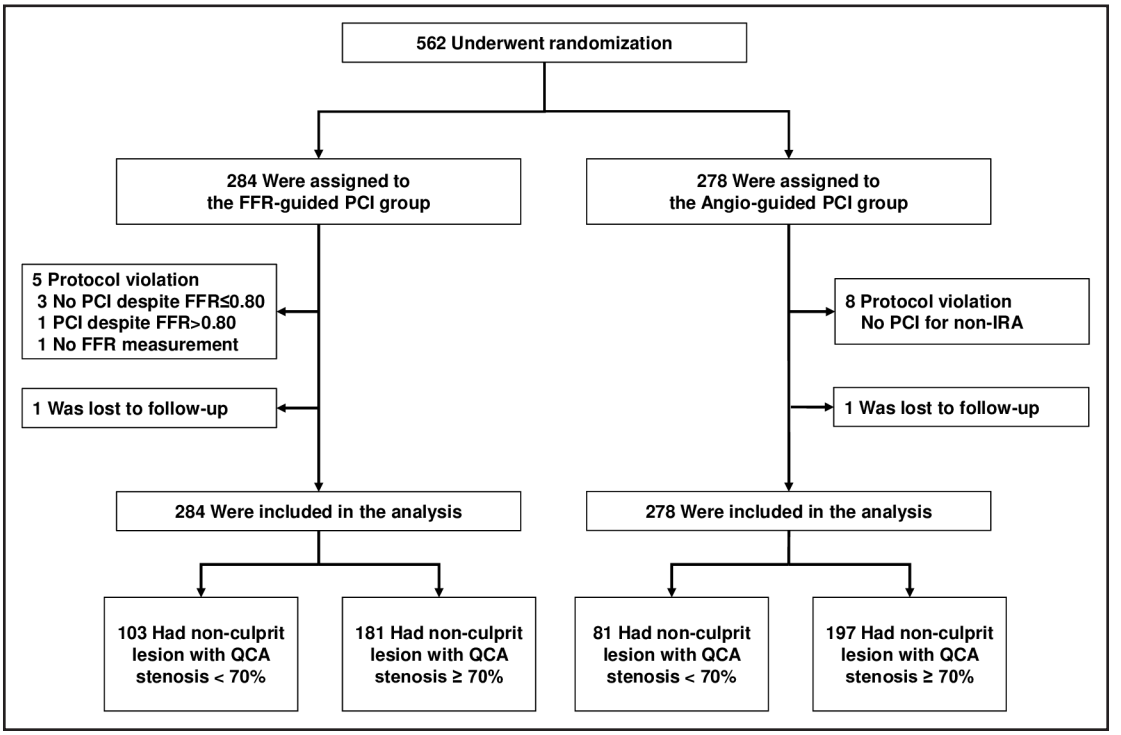

Figure 1. Study flow of quantitative coronary angiography substudy from the FRAME-AMI trial (Fractional Flow Reserve Versus Angiography-Guided Strategy for Management of Non-Infraction Related Artery Stenosis in Patients With Acute Myocardial Infarction).

FFR indicates fractional flow reserve; IRA, infarct-related artery; PCI, percutaneous coronary intervention; and QCA, quantitative coronary angiography.

Table 1. Baseline Demographic Characteristics

	QCA <70%				QCA ≥70%				*P* value*
	All (N=184)	Angio-guided PCI (n=81)	FFR-guided PCI (n=103)	*P* value	All (N=378)	Angio-guided PCI (n=197)	FFR-guided PCI (n=181)	*P* value	
Age, y	61.8±10.6	61.7±10.4	61.9±10.9	0.917	64.0±11.7	63.1±11.9	65.0±11.5	0.105	0.026
Male, n (%)	157 (85.3)	72 (88.9)	85 (82.5)	0.317	317 (83.9)	162 (82.2)	155 (85.6)	0.448	0.746
Body mass index, kg/m^2	24.8±3.4	24.5±3.8	25.1±3.1	0.288	24.8±3.1	25.0±3.2	24.5±3.0	0.081	0.778
Initial presentation, n (%)				0.338				0.734	0.002
ST-segment–elevation MI	115 (62.5)	47 (58.0)	68 (66.0)		182 (48.1)	97 (49.2)	85 (47.0)		
Non–ST-segment–elevation MI	69 (37.5)	34 (42.0)	35 (34.0)		196 (51.9)	100 (50.8)	96 (53.0)		
Hemodynamic data									
Systolic blood pressure, mm Hg	128.9±20.7	130.2±22.3	128.0±19.4	0.481	129.3±23.0	130±23.2	128.6±22.8	0.551	0.843
Diastolic blood pressure, mm Hg	78.5±13.7	78.9±13.5	78.3±13.9	0.751	77.5±15.6	77.2±15.5	77.9±15.6	0.67	0.42
Heart rate, beats/min	76.3±15.4	78.2±16.7	74.8±14.2	0.15	76.6±16.1	76.2±15.2	77.0±17.1	0.637	0.823
Symptom to door time, min									
ST-segment–elevation MI	282±341	230±278	333±390	0.979	228±396	187±244	270±504	0.469	0.281
Non–ST-segment–elevation	812±348	811±339	812±358	0.213	780±294	794±284	763±304	0.151	0.934
Door to balloon time, min									
ST-segment–elevation MI	120±220	74±52	165±299	0.604	118±210	131±252	105±155	0.29	0.952
Non–ST-segment–elevation MI	700±455	673±480	719±439	0.087	603±478	570±461	644±497	0.402	0.082
Medical history, n (%)									
Hypertension	97 (52.7)	42 (51.9)	55 (53.4)	0.952	206 (54.5)	110 (55.8)	96 (53.0)	0.658	0.759
Diabetes	54 (29.3)	20 (24.7)	34 (33.0)	0.286	129 (34.1)	66 (33.5)	63 (34.8)	0.874	0.299
Dyslipidemia	68 (37.0)	30 (37.0)	38 (36.9)	1	160 (42.3)	77 (39.1)	83 (45.9)	0.22	0.26
Current smoking	64 (34.8)	32 (39.5)	32 (31.1)	0.3	132 (34.9)	73 (37.1)	59 (32.6)	0.423	1
Family history of premature coronary artery disease	14 (7.6)	6 (7.4)	8 (7.8)	1	27 (7.1)	16 (8.1)	11 (6.1)	0.568	0.979
Chronic renal insufficiency	5 (2.7)	0 (0)	5 (4.9)	0.068	11 (2.9)	8 (4.1)	3 (1.7)	0.279	1
Previous stroke	7 (3.8)	4 (4.9)	3 (2.9)	0.701	17 (4.5)	11 (5.6)	6 (3.3)	0.415	0.874
Previous myocardial infarction	5 (2.7)	3 (3.7)	2 (1.9)	0.656	9 (2.4)	4 (2.0)	5 (2.8)	0.742	0.78
Previous PCI	11 (6.0)	4 (4.9)	7 (6.8)	0.758	26 (6.9)	16 (8.1)	10 (5.5)	0.428	0.824
Peripheral vessel disease	2 (1.1)	1 (1.2)	1 (1.0)	1	4 (1.1)	0 (0)	4 (2.2)	0.052	1
Atrial fibrillation	7 (3.8)	1 (1.2)	6 (5.8)	0.17	12 (3.2)	7 (3.6)	5 (2.8)	0.524	0.785
LV ejection fraction, %	54.0±10.1	53.7±11.2	54.3±9.2	0.725	53.1±9.9	53.6±9.8	52.6±10.1	0.319	0.306
Laboratory data									
Hemoglobin, g/dL	14.1±2.0	14.2±1.9	14.0±2.1	0.459	14.2±2.0	14.1±2.0	14.3±2.1	0.225	0.572
Creatinine, mg/dL	1.1±1.0	0.9±0.2	1.2±1.2	0.02	1.1±1.2	1.2±1.4	1.1±1.0	0.248	0.728
Glycated hemoglobin, %	6.4±1.3	6.1±0.8	6.5±1.6	0.063	6.5±1.3	6.5±1.2	6.6±1.4	0.613	0.239
Total cholesterol, mg/dL	179.9±47.8	176.8±50.2	182.3±46.0	0.454	180.1±45.0	179.2±43.3	181.1±46.8	0.69	0.963
HDL cholesterol, mg/dL	43.5±11.5	44.4±13.2	42.8±9.9	0.394	43.2±11.9	43.3±12.9	43.0±10.9	0.816	0.746
LDL cholesterol, mg/dL	119.9±42.7	117.2±44.6	122.1±41.1	0.462	120.4±44.2	120±46.9	120.8±41.2	0.867	0.909
Discharge medication, n (%)									
Aspirin	183 (99.5)	81 (100)	102 (99.0)	1	373 (98.7)	196 (99.5)	177 (97.8)	0.198	0.669
P2Y12 inhibitor									
Any	183 (99.5)	81 (100)	102 (99.0)	1	373 (98.7)	195 (99.0)	178 (98.3)	0.674	0.669
Clopidogrel	50 (27.2)	22 (27.2)	28 (27.2)	1	109 (28.8)	52 (26.4)	57 (31.5)	0.328	0.756
Ticagrelor	83 (45.1)	39 (48.1)	44 (42.7)	0.558	172 (45.5)	94 (47.7)	78 (43.1)	0.425	1
Prasugrel	50 (27.2)	20 (24.7)	30 (29.1)	0.614	92 (24.3)	49 (24.9)	43 (23.8)	0.894	0.534
Oral anticoagulant	6 (3.3)	2 (2.5)	4 (3.9)	0.696	13 (3.4)	5 (2.5)	8 (4.4)	0.471	1

(*Continued*)

Table 1. Continued

	QCA <70%				QCA ≥70%				*P* value*
	All (N=184)	Angio-guided PCI (n=81)	FFR-guided PCI (n=103)	*P* value	All (N=378)	Angio-guided PCI (n=197)	FFR-guided PCI (n=181)	*P* value	
β-blocker	137 (74.5)	62 (76.5)	75 (72.8)	0.685	294 (77.8)	159 (80.7)	135 (74.6)	0.191	0.443
ACE inhibitor or ARB	119 (64.7)	55 (67.9)	64 (62.1)	0.511	266 (70.4)	139 (70.6)	127 (70.2)	1	0.205
Statin	180 (97.8)	80 (98.8)	100 (97.1)	0.632	365 (96.6)	192 (97.5)	173 (95.6)	0.471	0.576

Data presented as mean±SD or as n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; FFR, fractional flow reserve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; and QCA, quantitative coronary angiography.

**P* value between QCA <70% and QCA ≥70%.

FFR-guided PCI group and 278 were assigned to the angiography-guided PCI group. QCA was performed on a total of 749 non-IRA lesions in these patients by the angiographic core laboratory. Of the 562 patients, 378 (67.2%) patients had at least 1 non-IRA lesion with QCA stenosis ≥70%, while 184 (32.7%) patients had non-IRA lesions with QCA stenosis <70%. The former group of 378 patients had 181 (47.9%) from the FFR-guided PCI group and 197 (52.1%) from the angiography-guided PCI group, while the latter group of 184 patients had 103 (56.0%) from the FFR-guided PCI group and 81 (44.0%) from the angiography-guided PCI group (Figure 1). The QCA ≥70% group had a higher mean age than the QCA <70% group. In the QCA ≥70% group, the proportion of patients with non–ST-segment–elevation MI was slightly higher than those with STEMI, while in the QCA <70% group, the proportion trend was the opposite. Both groups had a similar left ventricular ejection fraction and low-density lipoprotein cholesterol levels. The other baseline characteristics of the patients, including previous medical history, laboratory data, and discharge medications, were similar between the QCA ≥70% and QCA <70% groups (Table 1).

IRA/Non-IRA Interventions

In terms of the PCI for the IRA, the QCA ≥70% and QCA <70% groups had similar total numbers of lesions in the IRA, use of radial access, utilization of intravascular imaging, number of stents used per patient, mean diameter, and procedural success rate. However, the total length of stents used was longer in the QCA ≥70% group.

Regarding the procedural characteristics for non-IRA lesions, the total number of lesions in non-IRA, diameter stenosis of the most severe non-IRA lesion, number of arteries with at least 1 non-IRA lesion treated, stents used per patient, and total length of stents were higher in QCA ≥70% group, which corresponded to the higher complexity of non-IRA in the QCA ≥70% group. The mean FFR value of the most severe non-IRA was 0.70 in the QCA ≥70% group and 0.80 in the QCA <70% group. In both groups, FFR-guided PCI resulted in significantly lower rates of non-IRA PCI than angiography-guided PCI in both patients with QCA <70% group (QCA <70% group: 34.0% versus 93.8%, *P*<0.001; QCA ≥70% group: 81.2% versus 98.5%, *P*<0.001, respectively, for FFR-guided PCI and angiography-guided PCI). The complications during hospitalization were similar in both groups, as shown in Table 2.

Outcomes

At a median follow-up of 3.5 years (interquartile range, 2.7–4.1 years), the primary end point occurred in 58 of 562 patients, 18 from the FFR group and 40 from the angiography group (Kaplan-Meier event rates at 4 years, 7.4% versus 19.7%; HR, 0.43 [95% CI, 0.25–0.75]; *P*=0.003). FFR-guided PCI showed a lower risk of the primary end point than the angiography-guided PCI group among patients with QCA stenosis ≥70% (Kaplan-Meier event rates at 4 years, 8.5% versus 19.2%; HR, 0.41 [95% CI, 0.22–0.80]; *P*=0.022). Among patients with QCA stenosis <70%, FFR-guided PCI also showed a numerically lower risk of the primary end point than the angiography-guided PCI group (5.4% versus 12.1%; HR, 0.51 [95% CI, 0.14–1.89]; *P*=0.315; Table 3; Figure 2). There was no significant interaction between the treatment strategies and non-IRA stenosis severity for the risk of the primary end point (interaction, *P*=0.636). Regarding a composite of death and MI, FFR-guided PCI was consistently associated with a lower risk than angiography-guided PCI group in both groups of patients with QCA stenosis ≥70% (6.7% versus 15.1%; HR, 0.38 [95% CI, 0.19–0.78]; *P*=0.008) and with QCA stenosis <70% (1.0% versus 9.6%; HR, 0.08 [95% CI, 0.07–0.92]; *P*=0.042). There was no statistically significant difference in repeat revascularization, including IRA and non-IRA, in both QCA ≥70% and QCA <70% groups (Table 3). The absolute risk differences between PCI strategies of primary and secondary end points were similar according to QCA ≥70% and QCA <70% of non-IRA (Table S1).

DISCUSSION

The current substudy of the FRAME-AMI trial evaluated the comparative prognosis between FFR-guided and angiography-guided PCI according to non-IRA stenosis

Table 2. Baseline Procedural Characteristics

	QCA <70%				QCA ≥70%				
	All (N=184)	Angio-guided PCI (n=81)	FFR-guided PCI (n=103)	*P* value	All (N=378)	Angio-guided PCI (n=197)	FFR-guided PCI (n=181)	*P* value	*P* value*
Arteries with stenosis, n (%)				0.008				0.028	<0.001
2	138 (75.0)	69 (85.2)	69 (67.0)		207 (54.8)	119 (60.4)	88 (48.6)		
3	46 (25.0)	12 (14.8)	34 (33.0)		171 (45.2)	78 (39.6)	93 (51.4)		
Left main disease, %	2 (1.1)	1 (1.2)	1 (1.0)	1	16 (4.2)	4 (2.0)	12 (6.6)	0.05	0.083
SYNTAX score									
Baseline score, including infarct-related artery	16.5 (1.0–42.0)	11.5 (6.0–33.5)	14.5 (4.0–32.5)	0.212	17.0 (4.0–36.0)	17.0 (1.0–42.0)	19.0 (8.0–36.0)	0.12	0.14
Residual score, after noninfarct-related artery PCI	0.0 (0.0–15.0)	0.0 (0.0–15.0)	4.0 (0.0–10.0)	0.025	3.5 (0.0–15.0)	0.0 (0.0–13.5)	3.0 (0.0–15.0)	0.007	<0.001
Total number of lesions treated	1.8±0.7	2.0±0.7	1.6±0.6	<0.001	2.3±0.8	2.4±0.8	2.2±0.9	0.021	<0.001
Total number of stents used per patient	1.8±0.8	2.1±0.6	1.6±0.8	<0.001	2.6±1.0	2.7±0.9	2.5±1.0	0.034	<0.001
Median length of hospital stays, d	5.5±27.2	8.0±40.7	3.6±4.6	0.329	5.9±38.6	7.0±52.2	4.7±12.8	0.551	0.887
PCI of infarct-related artery									
Location of infarct-related artery, n (%)				0.53				0.516	0.012
Left anterior descending artery	67 (36.4)	33 (40.7)	34 (33.0)		128 (33.9)	72 (36.5)	56 (30.9)		
Circumflex artery	54 (29.3)	23 (28.4)	31 (30.1)		76 (20.1)	38 (19.3)	38 (21.0)		
Right coronary artery	63 (34.2)	25 (30.9)	38 (36.9)		174 (46.0)	87 (44.2)	87 (48.1)		
Total number of lesions in infarct-related arteries	1.1±0.4	1.1±0.3	1.2±0.4	0.066	1.1±0.3	1.1±0.3	1.1±0.3	0.817	0.183
Radial access, n (%)	155 (84.2)	66 (81.5)	89 (86.4)	0.48	316 (83.6)	163 (82.7)	153 (84.5)	0.741	0.943
Thrombus aspiration, n (%)	32 (17.4)	12 (14.8)	20 (19.4)	0.534	65 (17.2)	33 (16.8)	32 (17.7)	0.918	1
GP IIb/IIIa inhibitor use, n (%)	31 (16.8)	15 (18.5)	16 (15.5)	0.735	75 (19.8)	30 (15.2)	45 (24.9)	0.027	0.462
Treatment method, n (%)				0.162				0.234	0.124
Drug-eluting stent	179 (97.3)	81 (100)	98 (95.1)		374 (99.2)	195 (99.5)	179 (98.9)		
Drug-coated balloon angioplasty	3 (1.6)	0 (0)	3 (2.9)		1 (0.3)	1 (0.5)	0 (0)		
Aspiration thrombectomy only	2 (1.1)	0 (0)	2 (1.9)		2 (0.5)	0 (0)	2 (1.1)		
Intravascular imaging used, n (%)	47 (25.5)	20 (24.7)	27 (26.2)	0.948	75 (19.8)	39 (19.8)	36 (19.9)	1	0.153
Direct stenting, n (%)	16 (8.7)	12 (14.8)	4 (3.9)	0.019	34 (9.0)	15 (7.6)	19 (10.5)	0.424	1
Mean number of stents used per patient	1.2±0.5	1.2±0.4	1.2±0.6	0.701	1.3±0.5	1.2±0.5	1.3±0.5	0.397	0.249
Dimensions of stents, mm									
Mean diameter	3.1±0.5	3.2±0.6	3.1±0.4	0.035	3.2±0.5	3.1±0.5	3.2±0.5	0.506	0.448
Total length	32.5±16.5	30.7±12.0	34.0±19.3	0.162	37.0±16.9	36.4±16.3	37.6±17.5	0.488	0.003
Procedural success, n (%)	184 (100)	81 (100)	103 (100)	1	377 (99.7)	196 (99.5)	181 (100)	1	1

(*Continued*)

Table 2. Continued

	QCA <70%				QCA ≥70%				
	All (N=184)	Angio-guided PCI (n=81)	FFR-guided PCI (n=103)	*P* value	All (N=378)	Angio-guided PCI (n=197)	FFR-guided PCI (n=181)	*P* value	*P* value*
PCI of noninfarct-related artery									
Total number of lesions in noninfarct-related arteries	1.2±0.4	1.1±0.2	1.2±0.5	0.002	1.5±0.6	1.4±0.6	1.5±0.6	0.203	<0.001
Location of most severe noninfarct-related artery, n (%)				0.143				0.455	0.01
Left anterior descending artery	90 (48.9)	34 (42.0)	56 (54.4)		155 (41.0)	75 (38.1)	80 (44.2)		
Circumflex artery	41 (22.3)	18 (22.2)	23 (22.3)		132 (34.9)	71 (36.0)	61 (33.7)		
Right coronary artery	53 (28.8)	29 (35.8)	24 (23.3)		91 (24.1)	51 (25.9)	40 (22.1)		
Diameter stenosis of most severe noninfarct-related artery, %	62.0±5.9	63.7±4.9	60.8±6.3	0.001	82.2±8.3	82.2±8.2	82.1±8.3	0.853	<0.001
FFR value of most severe noninfarct-related artery	0.8±0.1		0.8±0.1		0.7±0.1		0.7±0.1		<0.001
Timing of noninfarct-related artery PCI				1				1	0.005
Immediate PCI during same procedure	126 (68.5)	55 (67.9)	71 (68.9)		211 (55.8)	110 (55.8)	101 (55.8)		
Staged intervention during same hospitalization	58 (31.5)	26 (32.1)	32 (31.1)		167 (44.2)	87 (44.2)	80 (44.2)		
At least 1 noninfarct-related artery treated, n (%)	111 (60.3)	76 (93.8)	35 (34.0)	<0.001	341 (90.2)	194 (98.5)	147 (81.2)	<0.001	<0.001
Treatment method, n (%)				1				0.35	0.135
Drug-eluting stent	110 (99.1)	75 (98.7)	35 (100)		323 (94.7)	181 (93.3)	142 (96.6)		
Drug-coated balloon angioplasty	1 (0.9)	1 (1.3)	0 (0)		17 (5.0)	12 (6.2)	5 (3.4)		
Plain balloon angioplasty	0 (0)	0 (0)	0 (0)		1 (0.3)	1 (0.5)	0 (0)		
Intravascular imaging used, n (%)	37 (33.3)	21 (27.6)	16 (45.7)	0.097	97 (28.4)	56 (28.9)	41 (27.9)	0.939	0.39
Mean number of stents used per patient	0.6±0.6	1.0±0.4	0.4±0.6	<0.001	1.3±0.8	1.5±0.7	1.2±0.9	0.003	<0.001
Dimensions of stents, mm									
Mean diameter	3.2±0.5	3.2±0.5	3.2±0.5	0.734	3.0±0.4	3.0±0.5	3.0±0.4	0.982	<0.001
Total length	29.8±13.1	27.7±12.6	34.2±13.2	0.017	41.2±22.2	40.4±21.9	42.4±22.6	0.425	<0.001
Procedural success, number (%)	111/111 (100)	76/76 (100)	35/35 (100)	1	335/341 (98.2)	190/194 (97.9)	145/147 (98.6)	0.626	0.344
Complications during hospitalization, n (%)									
Any complications	9 (4.9)	5 (6.2)	4 (3.9)	0.51	19 (5.0)	11 (5.6)	8 (4.4)	0.778	1
Congestive heart failure	2 (1.1)	2 (2.5)	0 (0)	0.192	3 (0.8)	3 (1.5)	0 (0)	0.249	0.664
Cardiogenic shock	3 (1.6)	2 (2.5)	1 (1.0)	0.583	5 (1.3)	2 (1.0)	3 (1.7)	0.674	0.721
Resuscitated cardiac arrest	1 (0.5)	1 (1.2)	0 (0)	0.44	1 (0.3)	1 (0.5)	0 (0)	1	0.548

(*Continued*)

Table 2. Continued

	QCA <70%				QCA ≥70%				
	All (N=184)	Angio-guided PCI (n=81)	FFR-guided PCI (n=103)	*P* value	All (N=378)	Angio-guided PCI (n=197)	FFR-guided PCI (n=181)	*P* value	*P* value*
Anaphylactic reaction to contrast agent	0 (0)	0 (0)	0 (0)	1	1 (0.3)	0 (0)	1 (0.6)	0.479	1
Access site bleeding	2 (1.1)	0 (0)	2 (1.9)	0.504	2 (0.5)	2 (1.0)	0 (0)	0.5	0.6
Nonaccess site bleeding	0 (0)	0 (0)	0 (0)	1	5 (1.3)	3 (1.5)	2 (1.1)	1	0.178
Peripheral embolization	0 (0)	0 (0)	0 (0)	1	1 (0.3)	1 (0.5)	0 (0)	1	1
Hospital-acquired infection	1 (0.5)	0 (0)	1 (1.0)	1	3 (0.8)	2 (1.0)	1 (0.6)	1	1
Arrhythmia	0 (0)	0 (0)	0 (0)	1	3 (0.8)	1 (0.5)	2 (1.1)	0.609	0.554

Data presented as mean±SD, median (interquartile range), or as n (%). Angio indicates angiography; FFR, fractional flow reserve; GP IIb/IIIa, glycoprotein IIb/IIIa; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

**P* value between QCA <70% and QCA ≥70%.

severity by QCA. The FFR-guided PCI group showed a lower risk of the primary end point than the angiography-guided PCI group in both patient groups, 1 with non-IRA stenosis severity of QCA ≥70% and the other with QCA <70% without significant interaction.

There have been several prior studies comparing IRA-only revascularization and complete revascularization in patients with AMI. PRAMI (Preventive Angioplasty in Acute Myocardial Infarction),[5] CvLPRIT (Complete Versus Lesion-Only Primary PCI),[6] COMPLETE (Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI)[3] trials compared angio-guided complete revascularization to IRA-only strategy and DANAMI 3 (Third Danish Trial in Acute Myocardial Infarction)-PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization),[12] COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel Disease)[13] compared FFR-guided complete revascularization to IRA-only strategy. These studies have proven the superiority of complete revascularization of non-IRA over the IRA-only revascularization and complete revascularization currently stands as recommended treatment in clinical guidelines.[14–16] Among the 4 studies that allowed angiography-guided PCI, 2 studies performed PCI on non-IRA lesions with angiographic diameter stenosis >50%, and the other 2 studies performed PCI on non-IRA lesions with angiographic diameter stenosis ≥70%. Both strategies for non-IRA PCI improved clinical outcomes compared with IRA-only PCI. Accordingly, performing PCI in non-IRA lesions, even with intermediate angiographic stenosis, may seem helpful for the prognosis of patients with AMI and multivessel disease. However, our study demonstrated that deferring intermediate and severe angiographic stenosis guided by FFR was safe and delivered better clinical outcomes compared with performing PCI for most of those lesions.

It is well known that the occurrence of myocardial ischemia does not depend on the severity of stenosis and can take place even in cases of moderate stenosis.[17] The gold standard for diagnosing lesion-specific myocardial ischemia being FFR, previous studies demonstrated that FFR-guided PCI could improve patient prognosis compared with angio-guided PCI or medical treatment.[18–20] However, there is a debate about whether FFR-guided PCI or angio-guided PCI has better results in treating non-IRA lesions. FRAME-AMI and FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) trials comparing angiography-guided PCI to FFR-guided PCI for patients with AMI and multivessel illness have shown inconsistent results.[9,21] Both trials defined eligible non-IRA lesions as 50% or more in diameter by visual assessment. The FLOWER-MI trial, which included 1171 STEMI patients with multivessel disease, found no statistically significant difference between the 2 strategies at 1 year.[21] Similarly, among patients randomly assigned to the angiography-guided PCI group, 560 of 577 (97.1%) patients underwent PCI in the FLOWER-MI trial and 270 of 278 (97.1%) patients underwent PCI in the FRAME-AMI trial. Also, in the FFR-guided PCI group, the number of patients who underwent PCI were 388 of 586 (66.2%) in FLOWER-MI and 182 of 284 (64.1%) in FRAME-AMI. However, a substudy of the FLOWER-MI study showed that among the patients who received complete revascularization guided by FFR measurement, those with ≥1 PCI (80% of non-IRA had FFR ≤0.80) had lower event rates at 1 year, compared with the patients with deferred PCI (98% of non-IRA had FFR >0.80).[22] This higher events rate among deferred non-IRA compared with treated

Table 3. Comparison of Clinical Outcomes According to Angiographic Stenosis of Nonculprit Lesion Among Patients With Myocardial Infarction

	Angio-guided PCI	FFR-guided PCI	Hazard ratio (95% CI)	*P* value
QCA <70% (n=184)	n=81	n=103		
Death, myocardial infarction, and repeat revascularization	9 (12.1)	4 (5.4)	0.51 (0.14–1.89)	0.315
All-cause death	7 (8.5)	1 (1.0)	0.09 (0.009–1.00)	0.051
Cardiac death	7 (8.5)	0 (0.0)	NA	NA
Myocardial infarction	2 (2.5)	0 (0.0)	NA	NA
Spontaneous myocardial infarction	1 (1.3)	0 (0.0)	NA	NA
Procedure-related myocardial infarction	1 (1.2)	0 (0.0)	NA	NA
Death and myocardial infarction	8 (9.6)	1 (1.0)	0.08 (0.07–0.92)	0.042
Repeat revascularization‡	2 (4)	3 (4.5)	1.01 (0.11–9.69)	0.991
Infarct-related artery	1 (1.3)	1 (2.6)	0.84 (0.05–13.5)	0.904
Noninfarct-related artery	2 (4.1)	2 (2.0)	0.89 (0.09–8.34)	0.918
QCA ≥70% (n=378)	n=197	n=181		
Death, myocardial infarction, and repeat revascularization	31 (19.2)	14 (8.5)	0.41 (0.22–0.80)	0.008
All-cause death	9 (6.5)	4 (2.8)	0.44 (0.14–1.43)	0.162
Cardiac death	8 (6.0)	3 (2.3)	0.36 (0.09–1.36)	0.13
Myocardial infarction	19 (9.4)	7 (3.9)	0.35 (0.14–0.83)	0.018
Spontaneous myocardial infarction	9 (4.4)	4 (2.2)	0.51 (0.15–1.68)	0.265
Procedure-related myocardial infarction	10 (5.1)	3 (1.7)	0.26 (0.07–0.96)	0.044
Death and myocardial infarction	27 (15.1)	11 (6.7)	0.38 (0.19–0.78)	0.008
Repeat revascularization‡	14 (9.2)	7 (4.1)	0.64 (0.25–1.62)	0.348
Infarct-related artery	7 (4.6)	3 (2.0)	0.57 (0.14–2.27)	0.426
Noninfarct-related artery	10 (6.4)	5 (3.0)	0.59 (0.2–1.75)	0.34

Data presented as n (%). Percentages are 4-y Kaplan-Meier estimates. Clinical end points were evaluated in the intention-to-treat population during the overall study period (ie, beginning from the time of randomization to the day of the first occurrence of an event, the day of the last office or phone visit, or the day of death during follow-up). Repeat revascularization includes all first clinically indicated elective, urgent, or emergent revascularization procedures that were not planned during index hospitalization during the overall study period. Angio indicates angiography; FFR, fractional flow reserve; NA, not available; PCI, percutaneous coronary intervention; and QCA, quantitative coronary angiography.

non-IRA, explain why the FFR-guided strategy PCI was not superior to the angiography-guided strategy in FLOWER-MI. Not only does this result differ from our result (Tables S2 and S3) but it is also inconsistent with the previous FFR substudy of the COMPARE-ACUTE trial, which showed that the clinical outcome of treated non-IRA was similar to that of untreated non-IRA with FFR ≥0.80.[23] In the FLOWER-MI trial, the procedural failure rate in non-IRA PCI was 4.7%, and 5 non-IRA PCI in the FFR-guided PCI group resulted in post-PCI TIMI flow grade of 0, which resulted in a higher number of procedure-related MI in the FFR-guided PCI group despite significantly less PCI was performed for non-IRA in the FFR-guided PCI group than the angiography-guided PCI group. Although the currently ongoing COMPLETE-2 study (https://www.clinicaltrials.gov; Identifier: NCT05701358) may provide clearer results, the FFR-guided PCI would be useful because angiography's overestimation of functional significance is exaggerated when considering non-IRA PCI in the acute setting in patients with AMI.[24]

In the current study, 147 of 181 (81.2%) patients with severe non-IRA (QCA ≥70%) and 35 of 103 (34.0%) patients with moderate non-IRA (QCA <70%) in the FFR-guided PCI group underwent PCI. Despite the FFR-guided PCI group having a procedure rate ≈20% lower than the angio-guided PCI group, FFR-guided PCI resulted in lower risk of the primary end point, as well as a composite of death and MI than angiography-guided PCI for patients with severe non-IRA. Although previous studies presented that a higher incidence of vulnerable plaque in non-IRA of patients with AMI than stable angina, our study results support that selective non-IRA PCI based on FFR would provide more favorable clinical outcomes than routine angiography-guided PCI for non-IRA lesions. Our findings are in line with the recently published quantitative flow ratio analysis of the FRAME-AMI trial.[25] In that study, 30.0% of non-IRA PCI in the angiography-guided PCI group was judged as unnecessary PCI based on quantitative flow ratio >0.80, whereas only 2.7% of non-IRA PCI in the FFR-guided PCI group was performed for non-IRA lesion with quantitative flow

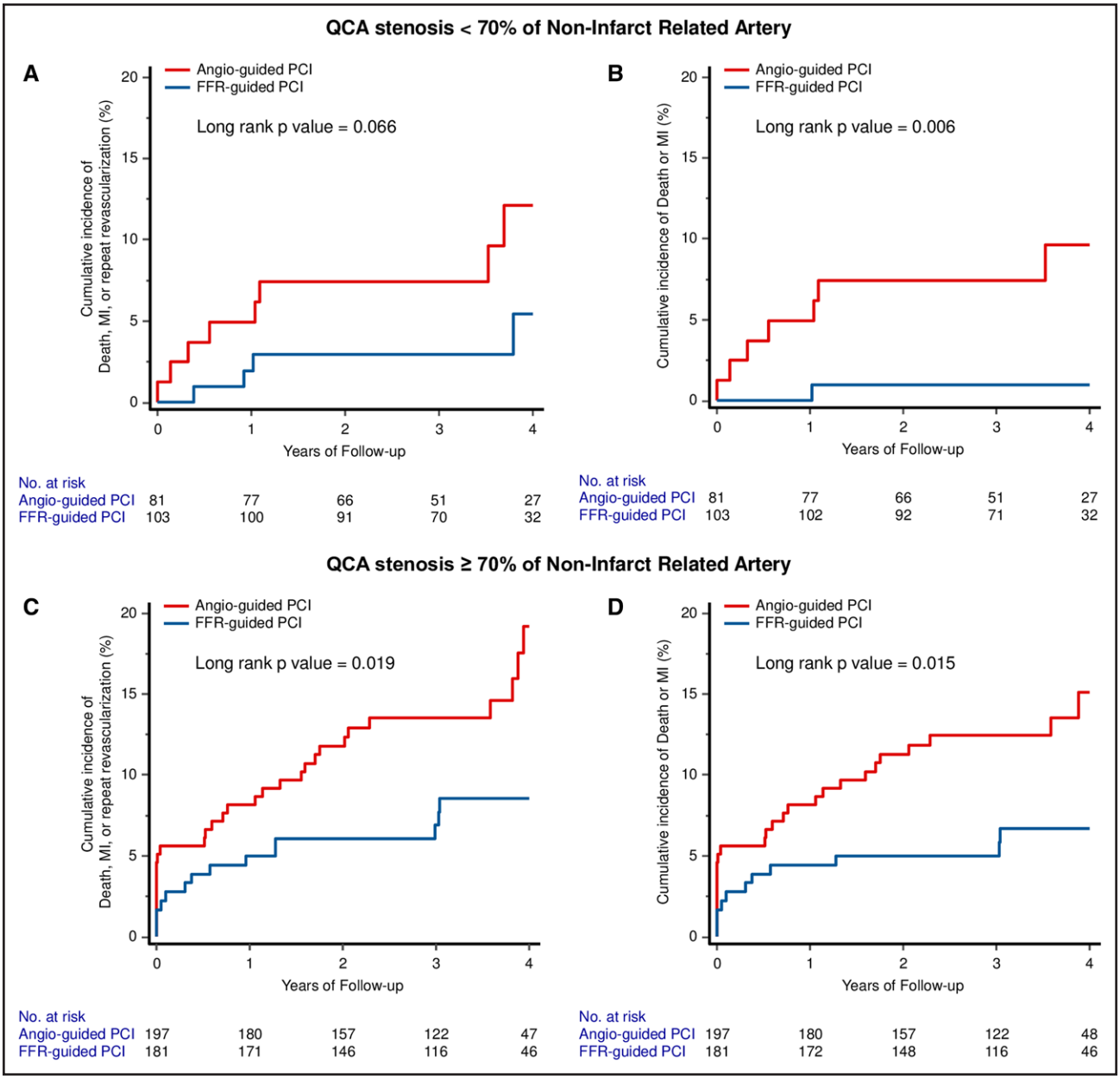

Figure 2. Cumulative incidence of the clinical outcomes by stenosis severity of noninfarct related artery.
Kaplan-Meier estimates of the cumulative incidence of (**A**) primary end point (a composite of time to death, myocardial infarction, or repeat revascularization) for quantitative coronary angiography (QCA) stenosis <70%. **B**, Death and myocardial infarction for QCA stenosis <70%. **C**, Primary end point for QCA stenosis ≥70%. **D**, Death and myocardial infarction for QCA stenosis ≥70%. Angio indicates angiography; FFR, fractional flow reserve; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

ratio >0.80. More importantly, patients who underwent non-IRA PCI for lesions with quantitative flow ratio >0.80 showed a significantly increased risk of adverse clinical events than those with deferred non-IRA PCI.

There are trials in which the benefits of non-IRA PCI were noticeably evident in stenosis above a certain degree. The prognostic benefits of non-IRA PCI were observed only in patients with non-IRA stenosis with QCA ≥60% (80% in visual assessment) in the COMPLETE trial[26] and in patients with 3-vessel disease and a non-IRA stenosis ≥90% in the DANAMI 3-PRIMULTI substudy.[27] Our results not only support but also are the extension of the findings in these trials by demonstrating that, regardless of angiographic severity, selective PCI only for functionally significant non-IRA is beneficial compared with routine PCI for angiographically stenosed non-IRA.

It should be noted that the current study was a post hoc analysis of a randomized controlled trial; therefore, there may be chances of false negatives due to inadequate power and false positives due to multiple testing. The benefits of FFR-guided PCI for non-IRA with moderate

or severe stenosis in patients with AMI and multivessel disease need to be confirmed in a prospective trial. The QCA of non-IRA was measured based on angiography in the acute setting of MI. Considering stenosis of non-IRA is exaggerated in the acute phase of MI compared with the stabilized phase, our result may not be applicable if coronary angiography of non-IRA and staged PCI after 1 month is planned. Also, the complexity of the non-IRA may have influenced the operators' decision on whether to include or exclude a patient. Moreover, the randomization process was not stratified according to the number of vessels involved, resulting in the difference in disease extent between the FFR-guided PCI and angiography-guided groups. However, the SYNTAX score was highest in the group of FFR-guided PCI and QCA ≥70%. The decision to perform PCI on non-IRA in patients with AMI would only be based primarily on a visual assessment of the coronary angiogram when non-IRA have complex lesion anatomy. However, if the non-IRA is eligible for FFR measurement, FFR-guided PCI of non-IRA is likely to improve the clinical outcome in patients with AMI and multivessel disease. This trial only included Korean patients, and the results may not be generally applicable to different ethnic groups.

In conclusion, the present FRAME-AMI substudy indicates that FFR-guided PCI poses a lower risk of primary end point than angiography-guided PCI regardless of the severity of non-IRA stenosis without significant interaction among patients with AMI and multivessel disease.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

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